Combinatorial Chemistry - An Online Journal 13 (2011) 33–35

Contents lists available at ScienceDirect

Combinatorial Chemistry - An Online Journal

journal homepage: www.elsevier.com/locate/comche

Combinatorial Chemistry Online

Volume 13, Issue 9, September 2011

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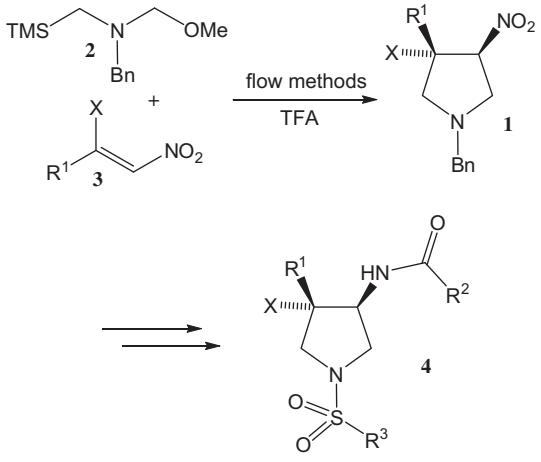
1. Current literature highlights

1.1. Synthesis of a drug-like pyrrolidine library by flow and parallel techniques

There continues to be a need for effective and rapid synthesis of drug-like compounds for high throughput screening. Ideally compounds need to be efficiently prepared in good yields and avoiding time-consuming purification steps. As part of a larger study of productive approaches to heterocyclic systems, a recent paper describes the use of a synergistic combination of flow and parallel synthesis to generate libraries of trisubstituted pyrrolidines.[1]

Flow synthesis has been shown to be an effective way of undertaking chemistry with careful control of heat and mass transfer. Furthermore, chemistry using hazardous reagents is better controlled as only small quantities of reactive intermediates are in the reaction vessel at any one time. The [3+2] cycloaddition has been shown to work especially well by flow methods, and nitropyrrolidines (**1**) can be made by flow synthesis from azomethines produced in situ. The H-Cube hydrogenation system can also be applied in series following the [3+2] dipolar cycloaddition for either reduction of a nitro group or the removal of a benzyl protecting group.

The pyrrolidine group is an important target for drug discovery as a number of pharmacologically active compounds such as Factor Xa inhibitors, NK_3 receptor antagonists and DPP-IV inhibitors all contain pyrrolidines. This recent publication describes the flow chemistry of commercially available *N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]benzylamine (**2**) with various nitroalkenes (**3**). The nitroalkene was introduced with TFA so as to catalyse the preparation of the intermediate dipole in situ. Following reaction, the reaction stream was collected and extracted with aqueous sodium bicarbonate to give the desired pyrrolidine products (**1**) in >80% yield. Alternatively, solid-supported scavenger reagents could be used to remove excess nitroalkene, TFA and coloured impurities, avoiding time-consuming batch workup protocols.



The synthetic route could be further modified by the connection of the H-Cube hydrogenation unit. Using a cartridge of Raney nickel as the reduction catalyst, the nitro group could be reduced, allowing acylation of the new amine. Alternatively, using 10% Pd on carbon in the H-Cube allowed removal of the benzyl protecting group allowing subsequent sulphonylation of the pyrrolidine nitrogen.

Using these synthetic options, a small drug-like pyrrolidine library (**4**) was constructed using a combination of flow techniques and parallel synthetic methods. One modification employed in the library synthesis was the use of tin (II) chloride for the reduction of the nitro group, thus avoiding the use of bulk quantities of Raney nickel. The compounds generated were profiled for log D, solubility, passive membrane permeability and metabolic stabilities.

2. A summary of the papers in this month's issue

2.1. Solid-phase synthesis

An efficient solid-phase synthetic approach for the synthesis of 2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine derivatives has been disclosed. The methodology is of value for the high throughput synthesis of potentially bioactive molecules.[2]

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doi:10.1016/j.comche.2011.07.002

2.2. Solution-phase synthesis

An efficient protocol for the one-pot preparation of alkyl 3-aryl-5-methylisoxazole-4-carboxylates from aryl aldehydes has been described. This method is readily amenable to the large scale preparation of isoxazoles as well as the parallel synthesis of isoxazole libraries.[3]

Boc-protected (piperazin-1-ylmethyl)biaryls have been synthesised from (Boc-piperazin-1-ylmethyl)phenylboronic acid pinacol esters via a microwave-mediated Suzuki–Miyaura coupling with aryl bromides. Judicial removal of the protecting group on the piperazine, or facile reduction of the nitro group on the biaryl system enabled the manipulation of two points of functionality in order to diversify the scope of the resulting biaryl library.[4]

A simple and efficient one-pot approach for assembling some fused spiro[4H-pyran-oxindole] heterocycles by means of three-component reactions between isatins, malononitrile or ethyl cyanoacetate, and 1,3-dicarbonyl compounds has been reported. The combinatorial syntheses were achieved for the first time without applying extra activation energy at ambient temperature while making use of $[BMIm]BF_4$ as an ionic liquid catalyst. Good functional group tolerance and broad scope of usable substrates are other prominent features of this methodology.[5]

A practical and general synthesis of 1,3,6-trisubstituted quinolin-4(1H)-ones starting from 1-alkyl-6-bromo-3-iodoquinolin-4(1H)-one has been described, based on regioselective sequential palladium-catalysed cross-coupling reactions under microwave irradiation. Good substrate generality, ease of execution and practicability make this method exploitable for the generation of libraries of chemically diverse 4-quinolones.[6]

An efficient, parallel synthesis of 2-substituted aminobenzimidazoles via intramolecular ring closing reactions of imidazolium ion tag immobilised *o*-phenylenediamine with various isothiocyanates has been developed. The ionic liquid-bound 2-substituted aminobenzimidazoles were cleaved from the support with sodium methoxide to generate the target compounds in good yields and high purities with two points of structural diversity.[7]

A series of 2-[(2-pyridylmethyl)sulphinyl]benzimidazole derivatives have been synthesised via a solution phase synthetic route using a reversal method of diversity introduction. Using this synthetic strategy, two key intermediates were delivered simultaneously, which allowed the introduction of diversity points onto the benzimidazole part of the final product under reliable reaction conditions. The compounds were used to identify potent H^+/K^+-ATP enzyme inhibitors.[8]

2.3. Scaffolds and synthons for combinatorial libraries

A diversity-oriented synthesis (DOS) protocol for scaffold discovery has been described. A general synthetic route was developed from a single lactam for access to various multi-functionalised spirocyclic keto-lactams and their derived spirocyclic keto-amines. This work provides the foundation for a sequential DOS strategy from scaffold discovery to drug discovery.[9]

2.4. Solid-phase supported reagents

A novel Merrifield resin-supported phenanthroline–Cu(I) complex has been developed and used as a highly efficient and recyclable catalyst in the reaction of 2-halobenzenamines with isothiocyanates for the synthesis of 2-aminobenzothiazoles. The reactions were applicable to a variety of 2-halobenzenamines and isothiocyanates, and generated the corresponding aminobenzothiazoles in good yields under mild reaction conditions. Moreover, the catalyst was quantitatively recovered from the reaction mixture by a simple filtration and reused for 10 cycles with almost consistent activity.[10]

2.5. Novel resins, linkers and techniques

To increase the source diversity of natural products, a new chemical library consisting of chemically modified microbial metabolites termed 'Unnatural Natural Products' has been generated. These compounds were obtained by chemical conversion of microbial metabolites in crude broth extracts followed by purification of reaction products with an LC–MS system. This library, revealed an XIAP inhibitor, C38OX6, which restored XIAP-suppressed enzymatic activity of caspase-3 in vitro.[11]

A class of glycolipopeptides for use as building blocks for a new type of dynamic combinatorial library has been reported. The members of the library consist of a variable carbohydrate moiety, coded amino acids, and lipoamino acids in order to generate amphiphiles. The head groups of amphiphiles are exposed on a micelle surface, providing entities which could be screened in biological assays to find the most potent combination of building blocks in order to identify new bioactive carbohydrate ligands.[12]

2.6. Library applications

An expedient four-step approach for the synthesis of a short library of original analogues of the Topo-I Luotonin-A inhibitor, substituted at the C_8- and N_{15}-positions, has been investigated. This approach consists of Rutaecarpines formation, their Witkop–Winterfeldt oxidation followed ultimately with functional adjustment of the pyrroloquinolone intermediates.[13]

A small library of 1-(isoquinolin-1-yl)guanidine has been constructed efficiently via a silver triflate-catalysed three-component reaction of 2-alkynylbenzaldehyde, sulphonohydrazide, with carbodiimide. The preliminary biological screens of these isoquinoline library members have been evaluated, and show promising results as PTP1B and HCT-116 inhibitors.[14]

The synthesis of a pyrimidinone library that targets anaplastic lymphoma kinase (ALK), an oncogenic receptor tyrosine kinase has been described. The library was generated in three steps from a versatile commercially available starting material, and some compounds within the library showed single digit micromolar inhibition of ALK in vitro, while showing minimal inhibition of other homologous insulin receptor family kinases.[15]

An efficient synthetic route to 1,5-disubstituted 2-aminoimidazoles from readily available amino acids and aldehydes has been developed. A library of simple analogues was synthesised and several compounds were shown to exhibit notable antibiotic activity against a variety of bacterial strains including multi-drug resistant isolates.[16]

A small library of bivalent α-D-mannopyranosides having rigid linkers has been constructed in order to evaluate the effects of inter-saccharide distances upon multivalent binding interactions with plant and bacterial lectins. To this end, iodoaryl and propargyl α-D-mannopyranosides were synthesised and the former treated with TMS-acetylene under palladium chemistry to provide their corresponding ethynylaryl derivatives. A library of 15 dimeric members was obtained using Lewis acid catalysed glycosidation, aryl–aryl homocoupling, transition metal catalysed Sonogashira cross-coupling reactions, and oxidative Glaser homocoupling.[17]

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Further reading

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